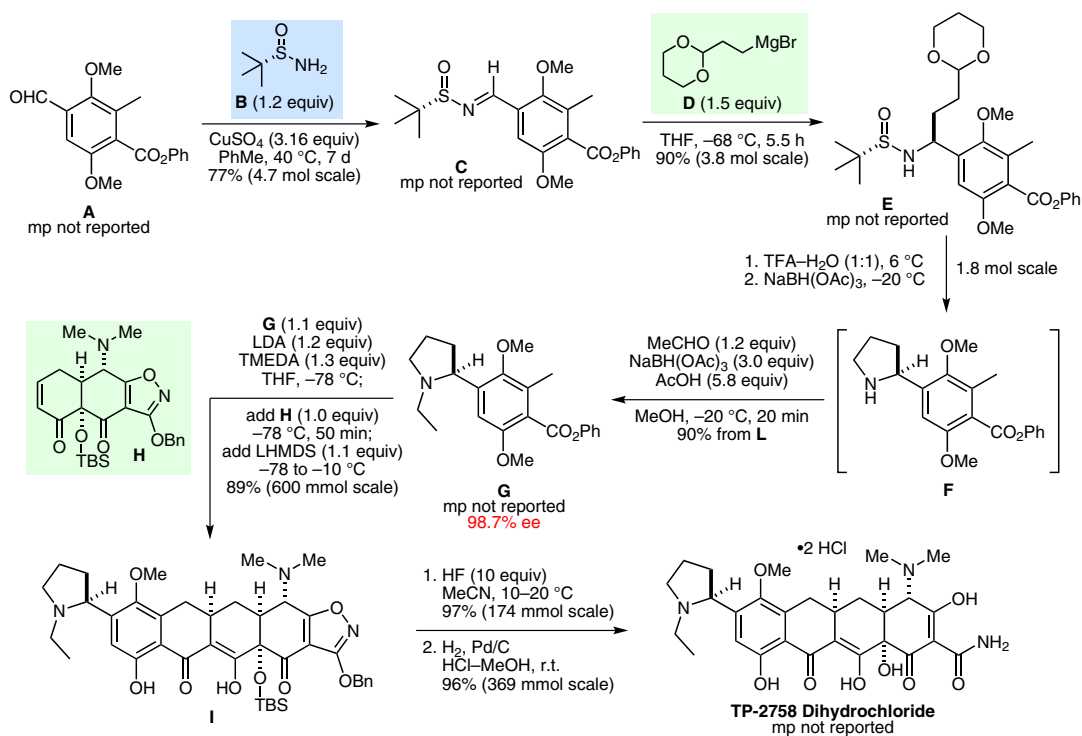
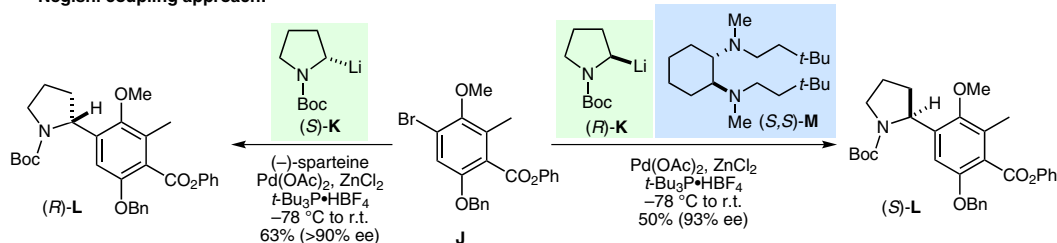


Synthesis of TP-2758



Negishi coupling approach:



Significance: TP-2758 is in development for the treatment of complicated urinary tract infections caused by Gram-negative pathogens. The closing stage of the synthesis depicted features the installation of the chiral pyrrolidine moiety in fragment **G** using Ellman's chiral sulfinamide auxiliary **B** (99% ee). The conjunction of complex fragments **G** and **H** using chemistry developed by Myers and co-workers (*J. Am. Chem. Soc.* **2008**, *130*, 17913) delivered the advanced intermediate **I** in 89% yield.

Comment: Enantioselective deprotonation of *N*-Boc pyrrolidine using *s*-BuLi and (-)-sparteine afforded the lithium reagent (*S*)-**K** that participated in a palladium-catalyzed Negishi coupling with bromoarene **J** to give enantioenriched pyrrolidine (*R*)-**L** in 63% yield (>90% ee). By using diamine (*S,S*)-**M** as a (+)-sparteine surrogate, the corresponding Negishi reaction delivered (*S*)-**L** in 50% yield (93% ee). Neither of these alternatives was robust, and the yields could not be improved.